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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/664,610	09/16/2003	Charles Wilson	23239-538 (ARC-38)	5499

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EXAMINER	
HUMPHREY, LOUISE WANG ZHIYING	

ART UNIT	PAPER NUMBER
1648	

MAIL DATE	DELIVERY MODE
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Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/664,610	WILSON ET AL.	
	Examiner	Art Unit	
	LOUISE HUMPHREY	1648	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *18 July 2011*.

2a)☐ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ An election was made by the applicant in response to a restriction requirement set forth during the interview on _____; the restriction requirement and election have been incorporated into this action.

4)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

5)☒ Claim(s) *127-132 and 134-137* is/are pending in the application.

5a) Of the above claim(s) _____ is/are withdrawn from consideration.

6)☐ Claim(s) _____ is/are allowed.

7)☒ Claim(s) *127-132 and 134-137* is/are rejected.

8)☐ Claim(s) _____ is/are objected to.

9)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

10)☐ The specification is objected to by the Examiner.

11)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

12)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

13)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

Continued Examination Under 37 CFR 1.114

A request for continued examination under 37 CFR 1.114, including the fee set forth in 37 CFR 1.17(e), was filed in this application after final rejection. Since this application is eligible for continued examination under 37 CFR 1.114, and the fee set forth in 37 CFR 1.17(e) has been timely paid, the finality of the previous Office action has been withdrawn pursuant to 37 CFR 1.114. Applicant's submission filed on 18 July 2011 has been entered.

DETAILED ACTION

In the prior action, mailed on 19 November 2010, claims 127-137 were pending and rejected.

This Office Action is in response to the amendment filed 18 July 2011, in which the Applicant amended claims 127, 134 and 135.

Claims 1-126 and 133 have been cancelled.

Claims 127-132 and 134-137 are pending and under consideration in the application.

The objection to the specification is withdrawn in view of Applicant's amendment.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. §103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the

> invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

(Prior Rejection – Maintained) The rejection of claims 127-130, 136 and 137 under 35 U.S.C. §103(a) as being unpatentable over Lupold et al. (US 6,933,114 B2, filed 16 October 2001) is maintained.

The instant claims are directed to a method for identifying an aptamer regulator comprising:

a) providing a target and a target partner that do not bind to each other in the absence of an aptamer regulator;

b) contacting a mixture of nucleic acids with the target and the target partner;

c) partitioning nucleic acids bound to a target-target partner (T/TP) complex from unbound nucleic acids, wherein binding of a nucleic acid to the target induces a conformational change in the target that increases the binding affinity of the target for the target partner relative to when the target is not bound by the nucleic acid;

d) retaining the nucleic acids bound to the T/TP complex;

e) removing the retained nucleic acids that are bound to the target in the T/TP complex, thereby identifying an aptamer that binds to a target, wherein binding of the aptamer to the target increases the binding affinity of the target for the target partner relative to when the target is not bound by the aptamer regulator.

The claim limitation of binding between a "target" and "target partner" reads on any interaction between a target and another molecule. The claim limitation of "aptamer regulator" reads on a nucleic acid ligand.

Claims 128 and 129 further limit the mixture of nucleic acids to a target-specific and diversified pool. Claim 130 further limits the target partner to be immobilized. Claim 136 further comprises the step of amplifying the retained nucleic acids and repeating steps a) to d). Claim 137 further comprises the step of screening the retained nucleic acids for a desired functional activity.

Lupold et al. discloses a basic method for identifying an aptamer comprising the steps of contacting a mixture of nucleic acids with the target, partitioning nucleic acids bound to target from the unbound nucleic acids, amplifying the retained nucleic acids (col. 8, lines 3-13), and repeating the partitioning/amplifying steps (col. 10, lines 22- 52). The candidate mixture is a mixture of nucleic acids of differing sequences with fixed sequences surrounding a randomized region (col. 10, lines 8-21). The fixed sequences can mimic a sequence known to bind to the target (col. 10, line 13-14), which renders the mixture of nucleic acids target-specific. Such randomized sequences are known in the art to render a diversified pool of nucleic acids as Lupold et al. also discloses the diversity of the structures employed by an aptamer library (col. 4, lines 43-44). Lupold et al. further discloses the step of screening the retained or identified nucleic acids for a desired functional activity such as the ability to inhibit NAALADase enzyme activity (col. 15, lines 63-64).

Lupold et al. does not ipsis verbis disclose a target partner and the desired functional activity of the aptamer binding to the target to increase the binding affinity of the target for the target partner relative to the unbound target.

However, Lupold et al. suggests that the basic aptamer selection method has been modified to achieve specific objectives (col. 10, lines 53-54) and further explicitly suggests nucleic acid ligands, often referred to as "aptamers," having desirable functions on a target including binding of the target, catalytically changing the target, reacting with the target in a way which modifies/alters the target or the functional activity of the target, facilitating the reaction between the target and another molecule (col. 7, lines 53-61), which means the same as the claim limitation of "an aptamer regulator that binds to a target wherein the aptamer binding increases the binding affinity of the target for the target partner relative to when the target is not bound by the aptamer regulator" in the instant claims.

It would have been obvious to one of ordinary skill in the art at the time the invention was made to modify the method of Lupold et al. so as to further include, in each method step, a target partner that does not bind the target without an agonist like the aptamer regulator. One having ordinary skill in the art would have been motivated to make such a modification to select for aptamers with the desirable functions of binding of the target, catalytically changing the target, reacting with the target in a way which modifies/alters the target or the functional activity of the target, and facilitating the reaction between the target and another molecule, as per the suggestion of Lupold et al.

Although Lupold etal. does not disclose immobilizing a target partner, Lupold et al. discloses immobilizing the target on a solid support (col. 8, lines 62-67 continued on to col. 9, line 6). It would have been obvious to one of ordinary skill in the art at the time the invention was made to modify the method of Lupold et al. so as to immobilize the

target partner rather than the target. One having ordinary skill in the art would have been motivated to make such a modification for the convenience of partitioning nucleic acid-bound target that is bound to the target partner.

There would have been a reasonable expectation of success, given the variety of modifications to the basic method that are routinely practiced by one of ordinary skill in the art, as disclosed by Lupold et al. (col. 10, lines 53 to col. 11, line 54). Thus, the invention as a whole was clearly prima facie obvious to one of ordinary skill in the art at the time the invention was made.

(Prior Rejection – Maintained) The rejection of claims 131-132 and 135 under 35 U.S.C. §103(a) as bein.q unpatentable over Lupold et al. (US 6,933,114 B2, filed 16 October 2001) in view of Geiger et al. (1996, of record in IDS filed 16 April 2010) is maintained.

The instant invention further comprises: (1) a negative selection prior to step (a) comprising partitioning and discarding nucleic acids bound to the target partner; and (2) the step of removing the retained nucleic acids from the target-target partner (T/TP) complex by eluting the nucleic acids with free excess target.

The disclosure of Lupold et al. is set forth above. Lupold eta/. does not disclose the prior step of negative selection or the step of eluting the nucleic acids with excess free target.

Geiger et al. discloses the step (1) of a negative selection with a non-desired target in which the pool of nucleic acids are partitioned and washed away with a non-

desired target, citrulline, prior to the selection of arginine-specific aptamers; and the step (2) of elution of arginine-specific aptamers with an excess of free target, a 20 mM solution of arginine (page 1030, right column, see the passage entitled "Selections").

It would have been obvious to one of ordinary skill in the art at the time the invention was made to modify the selection method disclosed by Lupold et al. so as to further include the step of negative selection with a non-desired target, such as the target partner in the instant case, and the step of eluting the nucleic acids with free excess target, as suggested by Geiger et al., with a reasonable expectation of success because this selection scheme and this elution technique are routine optimizations known in the art of aptamer selection. Thus, the invention as a whole was clearly prima facie obvious to one of ordinary skill in the art at the time the invention was made.

(Prior Rejection – Maintained) The rejection of claim 134 under 35 U.S.C. §103(a) as being unpatentable over Lupold et al. (US 6,933,114 B2, filed 16 October 2001) in view of Firer et al. (30 October 2001) is maintained.

The instant invention further comprises the step of removing the retained nucleic acids from the T/TP complex by eluting with an agonist competitor to the target.

The disclosure of Lupold et al. is set forth above. Lupold et al. does not disclose eluting the nucleic acids with an agonist competitor to the target.

Firer et al. discloses the strategy of competitive elution with excess ligands from a target molecule immobilized to a resin in a chromatography column (page 438, third complete paragraph).

It would have been obvious to one of ordinary skill in the art at the time the invention was made to modify the selection method disclosed by Lupold et al. so as to further include the step of eluting the nucleic acids with an agonist competitor to displace the nucleic acid ligands bound to the target, as suggested by Firer et al., with a reasonable expectation of success because competitive elution, an elution technique using a competitor for the same binding site on the target to remove the bound ligand, is a routine procedure that has been demonstrated in the art to separate the ligand from the target protein, as disclosed in Firer et al. Thus, the invention as a whole was clearly prima facie obvious to one of ordinary skill in the art at the time the invention was made.

Response to Arguments

Applicant's arguments set forth in the remark filed on 18 July 2011 have been fully considered but are not persuasive. Applicant's response has condensed the traversal of the three prior art rejections into one general discussion rather than directing arguments to each specific rejection. Applicant argues on page 18 that none of the three cited references teach or suggest that the target poorly binds or does not bind to the target partner in the absence of the aptamer regulator by asserting that the cited references do not teach any aptamers that can induce a conformational change in the target, let alone an aptamer that induces a conformational change in the target to increase the binding affinity of the target to its partner. Applicant individually argued against each reference. Applicant first argued that the first reference, the Lupold reference, merely describes aptamers that bind to Prostate-Specific Membrane Antigen

(PSMA) and does not teach or suggest an aptamer regulator that binds to or otherwise interacts with PSMA, nor does Lupold teach or suggest an aptamer regulator that can induce a conformational change in a target, like PSMA. Applicant next argued against the second reference by asserting that the Geiger reference fails to remedy the deficiencies in the Lupold reference because the Geiger reference merely describes aptamers that bind L-arginine with a high affinity. Applicant then argued against the third reference at the bottom of page 18 by asserting that the Firer reference merely describes the chemical effect of various elution buffers on protein-protein interactions. Applicant concluded on page 19 that there is no objective reason provided by the Lupold, Geiger and Firer references, alone or in combination, that would lead the skilled artisan to combine these references, nor is there any evidence that the resultant combination of these references would have been predictable from the teachings of these references or is there any reasonable expectation of success.

Applicant's principal argument is that the cited references do not expressly disclose the claimed intended use or desired function of binding of the nucleic acid to the target induces a conformational change in the target that increases the binding affinity of the target for the target partner, as recited in step c of claim 127. The Lupold reference however discloses the method comprising contacting nucleic acid mixture with the targets and screening the bound nucleic acids for the desired functional activity and further clearly suggests the modification to select for the desired functional activity of binding a target and increasing it's affinity for a target partner, albeit not expressly stated, by suggesting the desired functions of "binding of the target, catalytically

changing the target, reacting with the target in a way which modifies/alters the target or the functional activity of the target, facilitating the reaction between the target and another molecule." The "another molecule" would be the "target partner" in the instant case. The “binding of the target, catalytically changing the target, reacting with the target in a way which modifies/alters the target or the functional activity of the target" would encompass the “binding of a nucleic acid to the target induces a conformational change in the target that increases the binding affinity of the target for the target partner relative to when the target is not bound by the nucleic acid" as recited in the presently rejected claims. It would be reasoned from knowledge generally available to one of ordinary skill in the art that “binding of the target, catalytically changing the target” is the same process that “induces a conformational change in the target,” which is the structural change observed when a ligand is “reacting with the target in a way which modifies/alters the target or the functional activity of the target, facilitating the reaction between the target and another molecule,” which is the same result that “increases the binding affinity of the target for the target partner relative to when the target is not bound by the nucleic acid” as recited in the presently rejected claims.

In response to Applicant’s argument that there is no suggestion or motivation in any of the cited documents, the rationale to modify or combine the prior art does not have to be expressly stated in the prior art; the rationale may be expressly or impliedly contained in the prior art or it may be reasoned from knowledge generally available to one of ordinary skill in the art, established scientific principles, or legal precedent established by prior case law. See *In re Fine*, 837 F.2d 1071, 5 USPQ2d 1596 (Fed. Cir.

1988); *In re Jones*, 958, F2d 347, 21 USPQ2d 1941 (Fed. Cir. 1992). See also *In re Kotzab*, 217 F.3d 1365, 1370, 55 USPQ2d 1313, 1317 (Fed. Cir. 2000) (setting forth test for implicit teachings); *In re Eli Lilly & Co.*, 902 F.2d 943, 14 USPQ2d 1741 (Fed. Cir. 1990) (discussion of reliance on legal precedent); *In re Nilssen*, 851 F.2d 1401, 1403, 7 USPQ2d 1500, 1502 (Fed. Cir. 1988) (references do not have to explicitly suggest combining teachings); *Ex parte Clapp*, 227 USPQ 972 (Bd. Pat. App. & Inter. 1985) (examiner must present convincing line of reasoning supporting rejection); and *Ex parte Levengood*, 28 USPQ2d 1300 (Bd. Pat. App. & Inter. 1993) (reliance on logic and sound scientific reasoning).

"The test of obviousness is not express suggestion of the claimed invention in any or all of the references but rather what the references taken collectively would suggest to those of ordinary skill in the art presumed to be familiar with them." See *In re Rosselet*, 146 USPQ 183, 186 (CCPA 1965).

"There is no requirement (under 35 USC 103(a)) that the prior art contain an express suggestion to combine known elements to achieve the claimed invention. Rather, the suggestion to combine may come from the prior art, as filtered through the knowledge of one skilled in the art." *Motorola, Inc. v. Interdiqital Tech. Corp.*, 43 USPQ2d 1481, 1489 (Fed. Cir. 1997).

An obviousness determination is not the result of a rigid formula disassociated from the consideration of the facts of a case. Indeed, the common sense of those skilled in the art demonstrates why some combinations would have been obvious where others would not. See *KSR Int'l Co. v. Teleflex Inc.*, 82 USPQ2d 1385 (U.S. 2007)

("The combination of familiar elements according to known methods is likely to be obvious when it does no more than yield predictable results."). Applicant's assertion of the lack of predictable results lacks evidentiary basis. Neither did Applicant set forth any specific reasoning for the assertion.

Applicant's argument that the Geiger method does not disclose or suggest binding target, target partner and nucleic acids and inducing a conformational change that increases T/TP binding affinity is not germane to the rejection at issue. The Geiger reference is only cited to render obvious the negative selection step and the excess target elution step required by the dependent claims. The primary reference, Lupold, renders obvious the other claim elements for reasons set forth above.

Applicant's argument that the Firer method does not disclose or suggest binding target, target partner and nucleic acids and inducing a conformational change that increases T/TP binding affinity is not germane to the rejection at issue. The Firer reference is only cited to render obvious the competitive elution step with an agonist competitor as required by the dependent claim. The primary reference, Lupold, renders obvious the other claim elements for reasons already set forth above.

In summary, Applicant disagrees with Examiner's interpretation of the prior art disclosure as meaning the same as the claimed method steps and desired functions. Examiner does not find Applicant's arguments persuasive in absence of any objective evidence distinguishing the claimed method function/result from the prior art method function/result. Therefore, the invention as a whole was *prima facie* obvious to one of

ordinary skill in the art at the time the invention was made, as evidenced by the references, especially in the absence of evidence to the contrary.

Conclusion

No claim is allowable.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Louise Humphrey whose telephone number is 571-272-5543. The examiner can normally be reached on Mon-Fri, 9am-5pm.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Zachariah Lucas, can be reached on 571-272-0905. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

/Louise Humphrey/
Examiner, Art Unit 1648